~~Confidential~~

Helsinki, 25 October 2022

Addressees
Registrant(s) of JS_1843-05-6 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
13/06/2017

Registered substance subject to this decision ("the Substance")
Substance name: Octabenzone
EC number: 217-421-2

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***30 January 2026***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex VII of REACH

1. Long-term toxicity testing on aquatic invertebrates also requested below (triggered by Annex VII, Section 9.1.1., column 2).

B. Information required from all the Registrants subject to Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490);

2. Long-term toxicity testing on fish also requested below (triggered by Annex VIII, Section 9.1.3., column 2).

C. Information required from all the Registrants subject to Annex IX of REACH

1. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211);

2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210).

D. Information required from all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rabbit);

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) by oral route, in rats, specified as follows:
   - Ten weeks premating exposure duration for the parental (P0) generation;
   - The highest dose level in P0 animals must be determined based on clear

evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals as specified further in Appendix 1, or follow the limit dose concept. The reporting of the study must provide the justification for the setting of the dose levels;
- Cohort 1A (Reproductive toxicity); and
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

Reasons for the request(s) are explained in the following appendices:

- Appendices entitled "Reasons to request information required under Annexes VII to X of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

For certain endpoints, ECHA requests the same study from registrants at different tonnages. In such cases, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given. Only one study is to be conducted; the registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants under Article 53 of REACH.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix A: Reasons to request information required under Annex VII of REACH

1. Long-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Column 1 of Annex VII to REACH (Section 9.1.1.). However, long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

Information provided

You have provided two short-term toxicity studies on aquatic invertebrates similar to the OECD TG 202 but no information on long-term toxicity on aquatic invertebrates for the Substance.

Assessment of the information provided

We have assessed this information and identified the following issue:

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (Guidance on IRs and CSA, Section R.7.8.5).

In your technical dossier you report a saturation concentration of the Substance in water of <0.001 mg/L.

Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

In your comments to the draft decision you agree that the Substance has a very low water solubility and that therefore long-term testing might be triggered at Annex VII.

In your comments to the draft decision you further provide justification as to why testing could still be omitted. These comments are addressed under Appendix C.1.

The examination of the information provided, as well as the selection of the requested test and the test design are addressed under Appendix C.1.

Appendix B: Reasons to request information required under Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (Section 8.4.3.) in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

Triggering of the study

Your dossier contains negative results for both a Bacterial reverse mutation assay (OECD TG 471, 1991) and an *In vitro mammalian chromosome aberration test* (OECD TG 473, 2001), both with negative results. Therefore, the information requirement is triggered.

Information provided

You have adapted this information requirement by using a Grouping of substances and read-across approach and provided the following information:

(i) Summary of an *in vitro* mammalian cell gene mutation test on the analogue substance (2-hydroxy-4-methoxyphenyl)(phenyl)methanone (EC No.205-031-5) from the following publication Seifried *et al.* (2006), A Compilation of Two Decades of Mutagenicity Test Results with the Ames Salmonella typhimurium and L5178Y Mouse Lymphoma Cell Mutation Assay*. Chem. Res. Toxicol.* 19: 627-644.

Assessment of information provided

We have assessed this information and identified the following issue(s):

Read-across adaptation rejected

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

We have identified the following issue(s) with the prediction of toxicological properties:

Absence of read-across documentation

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the study(ies) on the source substance(s) (Guidance on IRs and CSA, Section R.6.2.6.1.).

You have provided an endpoint study record entitled 'read-across justification', however the study record does not contain a justification for your adaptation. In addition, you have provided a robust study summary for study (i) conducted with a substance other than the

Substance in order to comply with the REACH information requirements. However, you have not provided documentation as to why this information is relevant for the Substance.

In the absence of such documentation, the properties of the Substance cannot be reliably predicted from the data on the source substance.

Adequacy and reliability of study on the source substance

Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG OECD TG 476 or OECD TG 490. Therefore, the following specifications must be met:

a) The maximum concentration tested must induce 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
b) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the response compared with the concurrent negative control.
c) Data on the cytotoxicity and the mutation frequency for the treated and control cultures must be reported.

The reported data for the OECD TG 476, study (i), you have provided do not include:

a) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that the maximum concentration tested induced 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. In the study concentrations up to 50 and 52 µg/mL, with and without S9 respectively, were used. The highest concentration tested was not limited by cytotoxicity or precipitation. It should also be noted that the Substance could be tested up to 816 µg/mL in the *in vitro* mammalian chromosome aberration test (OECD TG 473, 2001).
b) one positive control that produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control. The study has a positive control which is reported to have returned valid results; however no statistical analysis of the response obtained from this control is provided.
c) data on the cytotoxicity and the mutation frequency for the treated and control cultures. The study contains average values for mutation frequency and relative growth; however no statistical analysis is provided for each of these parameters.

The information provided does not cover key parameter(s) required by OECD TG 476.

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s).

Therefore, your read-across approach under Annex XI, Section 1.5. is rejected and the information requirement is not fulfilled.

Study design and test specifications

To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

In your comments to the draft decision, you agree to conduct the requested study with the Substance.

2. Long-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Column 1 of Annex VIII to REACH (Section 9.1.3.). However, long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble.

Information provided

You have provided an OECD TG 203 study as well as two short-term toxicity studies on fish similar to the OECD TG 203 but no information on long-term toxicity on fish for the Substance.

Assessment of the information provided

We have assessed this information and identified the following issue:

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (Guidance on IRs and CSA, Section R.7.8.5).

As already explained under Section A.1, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

In your comments to the draft decision you agree that the Substance has a very low water solubility and that therefore long-term testing might be triggered at Annex VIII.

In your comments to the draft decision you further provide justification as to why testing could still be omitted. These comments are addressed under section C.2.

The examination of the information provided, as well as the selection of the requested test and the test design are addressed under section C.2.

Appendix C: Reasons to request information required under Annex IX of REACH

1. Long-term toxicity testing on aquatic invertebrates

Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

Information provided

You have provided the following justification to omit the study:

"*An environmental exposure assessment was performed in order to determine possible risks of the test compound to all environmental compartments. According to the results of the exposure assessment, all the relevant uses of the test substance are considered to be safe with a Risk Characterization Ratio below 1. Therefore, studies on the long term toxicity to aquatic invertebrates are not provided*."

Assessment of the information provided

While you have not explicitly indicated the legal basis of your adaptation, ECHA understands that you are referring to Annex IX, Section 9.1, Column 2.

We have assessed this information and identified the following issue:

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on aquatic organisms than the standard information, if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Your adaptation is therefore rejected.

In the comments to the draft decision you clarified that you intend to adapt this information requirement according to REACH Annex XI, Section 3.1..

You claim that:

- A PNEC can be derived from the data already available and that the increased uncertainty due to the lack of long-term toxicity data would be fully taken into account by the standard safety factor used. You consider PNEC derivation as conservative and explain that, as a worst case, the EC50 value of 52 mg/L derived from a *Daphnia magna* study using an emulsifier has been used as starting point.
- RCRs, as a measure of comparison of this PNEC with PECs from exposure assesments covering all relevant uses of the Substance's life cycle, are always below 1.

ECHA understands that for your adaptation you are specifically relying on REACH Annex XI Section 3.2 (a).

In your comments, you further indicate that the Substance has already been evaluated under the substance evaluation process and that during this evaluation a need for further long-term testing in aquatic species was not identified.

Under Annex XI, Section 3, testing in accordance with Annex IX may be omitted based on the exposure scenario(s) developed in the Chemical Safety Report. The justification must be based on a rigorous exposure assessment in accordance with Annex I, Section 5. As regards to Section 3.2(a) The following criteria must be met:

i. the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses referred to in Annex VI, Section 3.5.;

ii. a PNEC can be derived from available data, which:

- must be relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes and therefore must be based on reliable information on the hazardous properties of the substance on at least three trophic levels.
- must take into account the increased uncertainty resulting from the omission of the information requirement, in this case by selecting an appropriate assessment factor (AF) as described in Guidance on IRs and CSA, Section R.10.3.

iii. the ratio between the results of the exposure assessment (PECs) and the PNEC are always well below 1.

For the reasons explained under requests A.1 and B.2, short-term tests do not give a true measure of toxicity for poorly water soluble substances and therefore the long-term tests on Daphnia and fish are required for hazard assessment of the Substance. Without the information on long-term toxicity to aquatic invertebrates as well as fish, a reliable $PNEC_{aquatic}$ cannot be derived. The EC50 you use to derive a $PNEC_{aquatic}$ originates from a short-term toxicity study with daphnia and is not an adequate basis for $PNEC_{aquatic}$ derivation of poorly water soluble substances, like the Substance. Moreover, this particular EC50 value is higher than the water solubility of the Substance and it stems from a 24h exposure duration which is even shorter than the exposure duration of 48h for short-term toxicity testing in aquatic invertebrates according to the OECD TG 202. Therefore, your considerations in terms of this value claiming that it would reflect a worst-case are not justified.

In conclusion, you have not demonstrated that an appropriate PNEC can be derived and therefore the condition of Annex XI, Section 3.2(a)(ii) is not met.

Further, ECHA notes that substance evaluation and compliance check are regulatory processes that, in general, differ in their objectives. Whilst the compliance check of a registration dossier normally aims at verifying whether a registration dossier complies with the applicable information requirements, the objective of substance evaluation is to clarify the potential risks that a substance poses to human health or the environment. Therefore, the respective process might come to a different conclusion on the need to provide information. As explained above, neither the information provided in your dossier nor the justification you provide in your comments to the draft decision fulfill the information requirement. Therefore, there is a data gap and the information requirement is not fulfilled.

Study design and test specifications

The Substance is difficult to test due to the low water solubility (<0.001 mg/L). The OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in the OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in the OECD TG 211. In case a dose-response relationship cannot be established

(no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

2. Long-term toxicity testing on fish

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

Information provided

You have provided the following justification to omit the study:

"*No toxic effects were observable in an acute study of the test substance on Brachydanio rerio ([redacted] 1988a). This result is supported by another short term study on orange-red killifish (MITI 1992). Furthermore, an environmental exposure assessment was performed in order to determine possible risks of the test compound to all environmental compartments. According to the results of the exposure assessment, all the relevant uses of the test substance are considered to be safe with a Risk Characterization Ratio below 1. Due to this calculations, the lack of toxic effects in the acute studies, and for reasons of animal welfare, the risk to fish is expected to be low and long term studies are not provided*."

Assessment of the information provided

While you have not explicitly indicated the legal basis of your adaptation, ECHA understands that you are referring to Annex IX, Section 9.1, Column 2.

We have assessed this information and identified the following issue:

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for providing further information on long-term toxicity to fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

Your adaptation is therefore rejected and the information requirement is not fulfilled.

In your comments to the draft decision you raise the same considerations as already indicated under request C.1.

In addition, you refer again to animal welfare reasons to omit further testing.

As explained under request C.1., neither the information provided in your dossier, nor the adaptation under Annex XI Section 3.2 (a) that you provide in your comments on the draft decision, fulfill the information requirement.
In addition, as stated above, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

Therefore, the information you submitted in both your dossier and your comments on the draft decision does not fulfil the standard information requirement and there is a data gap that must be fulfilled.

Study design and test specifications

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (Guidance on IRs and CSA, Section R.7.8.2.).

The OECD TG 210 specifies that, for difficult to test substances, the OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix C.1.

Appendix D: Reasons to request information required under Annex X of REACH

1. Pre-natal developmental toxicity study in a second species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X to REACH.

Information provided

You have provided:

(i) Pre-natal developmental toxicity study in rats (OECD TG 414, 2017);
(ii) Waiver developmental toxicity 2nd species: "*This information will be submitted later based on ECHA decision number SEV-D-2114303201-75-01/F. The MSCA will evaluate the need to request further information in order to clarify the concern. The dossier will be updated once this information is available*".

Assessment of the information provided

We have assessed this information and identified the following issue(s):

In order to be compliant and enable concluding if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 for studies in two species. A pre-natal developmental toxicity study in a second species is a standard information requirement at Annex X unless one or more of the adaptations in Section 8.7 of Annex X or Annex XI apply, taking into account the results of the test in the first species or any other relevant avalable information.

You have not provided any study information in a second species.

In addition, ECHA notes that decision SEV-D-2114303201-75-01/F did not request any information relating to developmental toxicity.

Based on the above, the information you provided does not fulfil the information requirement.

Study design and test specifications

A PNDT study according to the OECD TG 414 should be performed in the rabbit or rat as the preferred species. The test in the first species was carried out by using a rodent species (rat). Therefore, a PNDT study in a second species must be performed in the rabbit as preferred non-rodent species.

The study must be performed with oral[2] administration of the Substance.

In your comments to the draft decision, you agree to conduct the requested study with the Substance.

2. Extended one-generation reproductive toxicity study

An extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex X to REACH (Section 8.7.3.).
Information provided
You have provided:

(i) A modified OECD TG 422 study (2017) with the Substance. The study includes a 10-week pre-mating exposure period;

[2] ECHA Guidance R.7a, Section R.7.6.2.3.2.

(ii) A multi-generation study (1969) with the Substance.

Assessment of the information provided

We have assessed this information and identified the following issue(s):

Study/Studies not adequate for the information requirement

(Eco)toxicological studies must comply with a recognised test method (Art. 13(3) of REACH), in this case the OECD TG 443. Such study must cover the key parameters of the corresponding OECD test guideline (Art. 13(3) of REACH). Therefore, the following specifications must be met:

a. 20 pregnant females for each test and control group;
b. Examinations of relevant life stages, including the extensive postnatal investigations of the fully exposed F1 generation up to the adulthood.
c. Examination of systemic toxicity of the P0 generation

The study (i) is described as "*as a modified reproduction/developmental toxicity screening test*". This study has been conducted using the OECD TG 422 which is a screening test rather than a conclusive test for toxicity to reproduction. In any case, that study does not cover the key parameters of the OECD TG 443 such as:

a. A statistical power equivalent to the OECD TG 443, as the study started with 12 mating-pairs in each group which resulted in 10-12 pregnant females.
b. Extensive postnatal investigations of the fully exposed F1 generation up to adulthood are not included.

The study (ii) is described as "a multigeneration study". That study does not cover the key parameters of the OECD TG 443 such as:

a. A statistical power equivalent to the OECD TG 443, as the study started with 16 mating-pairs in each group which resulted in 13-16 pregnant females.
b. Extensive postnatal investigations of the fully exposed F1 generation up to adulthood are not included.
c. The study has not investigated systemic toxicity of the P0 generation to the extent required by the OECD TG 443.

The studies are not adequate for the information requirement.

Should the two studies be combined in a weight of evidence approach, point a) would no longer apply. However, combining the studies would not mitigate the deficiencies in the coverage of the parameters listed under points b) and c).

In your comments on the draft decision, you do not agree to conduct the study.

You argue that the Substance has already been assessed under substance evaluation and the concerns have been addressed. As already explained in Appendix C, Section 1, the scope of the substance evaluation process is different from that of a compliance check.

The substance evaluation decision on the Substance requested a pre-natal developmental toxicity study (OECD TG 414) and a Range finding study for an extended one generation reproductive toxicity study (based on OECD TG 422).

You have provided the requested studies.

Based on this information the evaluating MSCA concluded that the requested information was provided, that no effects on fertility and on offspring in the OECD TG 422 study was observed and that no maternal or developmental toxicity was detected in the OECD TG 414 study. The MSCA considered that the concerns were clarified and that no additional information was needed under substance evaluation.

However, this does not mean that the registration dossier for the Substance has been made compliant with the REACH information requirements. The Substance is registered above 1000 tonnes per annum and subject to Annex X information requirements which includes an extended one-generation reproductive toxicity study (OECD TG 443).

In addition, you provide an argumentation which could be interpreted as a weight of evidence adaptation although you do not explicitly refer to the legal basis for such adaptation under Annex XI, Section 1.2.

You bring forward the following sources of information:
(i) A modified OECD TG 422 study (2017) with the Substance.
(ii) A multi-generation study (1969) with the Substance.

ECHA has already assessed this information concluded that none of these sources of information, individually or together, are adequate to fulfil the information foreseen to be obtained from an extended one-generation reproductive toxicity study (see reasons above).

You also bring forward the following additional sources of information:
(iii) Pre-natal developmental toxicity study in rats (2017) with the Substance.
(iv) Several repeated dose toxicity studies; available in IUCLID section 7.5.
(v) Several *in vitro* mechanistic studies investigating potential endocrine activity of the Substance; available in IUCLID section 7.9.

ECHA has assessed this information:

The pre-natal developmental toxicity study does not, due to its study design, bring relevant information on effects occurring before implantation or after one day prior to the scheduled delivery. However, it provides relevant information on maternal toxicity and maintenance of pregnancy.

The repeated dose toxicity studies have different exposure durations and were conducted in rats and dogs. These studies provide relevant information regarding systemic toxicity of the parental (P0) generation. However, the reliability of the contribution of the results obtained from these studies to the weight of evidence depends on the dosing and exposure duration used in the studies. In addition, the females were not pregnant and pregnant animals may be more sensitive.

The *in vitro* mechanistic studies investigating potential endocrine activity of the Substance does not investigate any of the key parameters of the OECD TG 443. Therefore, these studies do not bring relevant information with regards to a weight-of-evidence adaptation for this information requirement.

However, endocrine disruptive properties is one of the criteria for expanding the study design of the OECD TG 443. In this context ECHA has already considered the information.

ECHA concludes that the additional sources of information provide some additional infromation relevant to point c. above, i.e. systemic toxicity of the P0 generation. However,

none of the additional sources of information provide any information on point b. above, i.e. extensive postnatal investigations of the fully exposed F1 generation up to adulthood.

In addition, the weight of evidence justification brought forward in the comments is not according the requirements of Annex XI, Section 1.2.

Annex XI, Section 1.2. requires a reasoned justification which explains why information from several independent sources together enable a conclusion on the information requirement. This justification must explain how the individual sources of information are weighted and how all the sources of information together enable a conclusion on each of the key parameters foreseen by the study normally required for the information requirement.

According to the Guidance on IRs and CSA, Section R.4, the weight given to the sources of information is influenced by the reliability of the data, consistency of results, nature and severity of effects, and relevance and coverage of the information for the given information requirement. The reliability of the data is strongly linked to the method used to generate the information. Therefore, aspects such as exposure duration, dose-levels used, and the statistical power of the study affect the weight of the individual sources of information.

Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be integrated in order to decide whether they together provide sufficient weight to conclude whether the Substance has or has not the (dangerous) property investigated by each of the key parameters foreseen by the study normally required for the information requirement. As part of the overall conclusion, an assessment of the residual uncertainty is also required.

You have not weighted the individual sources of information nor provided a clear and transparent assessment of to which extent the sources of information cover each of the key parameters foreseen by the study normally required for the information requirement.

Based on the above, the information you provided does not fulfil the information requirement.

Study design and test specifications

Premating exposure duration and dose-level setting

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration.[1]

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and must be included.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and/or Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[3].

[3] ECHA Guidance R.7a, Section R.7.6.

Appendix E: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[4].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals

Appendix F: Procedure

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 25 January 2021.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the requests.

Deadline to provide the information

In your comments on the draft decision, you requested an extension of the deadline to provide the information from 24 months to 42 months from the date of adoption of the decision.

You refer to limited laboratory capacity for all requested tests.

For the aquatic toxicity studies in particular, you indicate that the Substance is difficult to test due to the low water solubility. You justify the request for an extension due to the need to conduct a preliminary solubility test and due to the expected challenges in development of an adequate analytical method for exposure concentration monitoring. Furthermore, you consider that the environmental tests should be conducted in a tiered manner.

For reproductive toxicity, you indicate that 32 months is required to conduct both studies sequentially taking into account laboratory capacity, need for dose-range finding studies and experience from other substances.

ECHA took into account this information and the provided documentary evidence. The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

The timelines given in the initial draft decision have already considered sequential testing where appropriate. Therefore, no additional time is granted for tiered testing.

Based on the above, ECHA has extended the deadline with 12 months from 24 to 36 months from the adoption of the decision.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposal(s) for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s) and referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee unanimously agreed on the draft decision during its MSC-79 meeting. ECHA adopted the decision under Article 51(6) of REACH.

Appendix G: List of references - ECHA Guidance[6] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[8]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

OECD Guidance documents[9]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

[9] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix H: Addressees of this decision and their corresponding information requirements

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.